

Adrenocortical tumours: challenges and recent advances in diagnosis and treatment

Ronchi, Cristina

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Special Issue of the Journal *Minerva Endocrinologica*

“Unilateral non-aldosterone producing adrenocortical tumors”

Title: Adrenocortical tumours: challenges and recent advances in diagnosis and treatment

Editorial

^{1,2,3}Cristina L. Ronchi

¹Institute of Metabolism and System Research, University of Birmingham, United Kingdom; ²Centre for Endocrinology, Diabetes and Metabolism (CEDAM), Birmingham Health Partners; ³Division of Endocrinology and Metabolism, University Hospital of Wuerzburg, Wuerzburg, Germany.

Unilateral adrenocortical tumors consist in frequent benign adrenocortical adenomas (ACA) and rare malignant adrenocortical carcinomas (ACC). On one side, ACAs are among the most common human neoplasia with a reported prevalence of 2-10% in the general population. They are generally endocrine inactive and clinically unapparent, thus being often incidentally-discovered. However, in 30% of cases ACAs may be associated with autonomous steroid (cortisol or aldosterone) secretion and clinical syndromes that may induce severe morbidities and even increase mortality (1, 2). On the other side, ACC are extremely rare cancers with a usually aggressive clinical outcome (mean 5-year survival rate 20-50%), mostly depending on initial tumour stage (3) and other clinical or histopathological parameters, such as the ki67 proliferation index (4, 5). For this reason it is important to precociously differentiate ACC from ACAs. Nowadays, the differential diagnosis mostly relies on a series of histopathological malignant criteria included in the Weiss score. Nevertheless, some cases still remain undefined (6), so that we are still looking for reliable diagnostic markers that may allow to precisely differentiate benign from malignant adrenocortical tumours. For instance, new techniques have been proposed, such as the urine steroid metabolome analysis (7), but their role in a routine setting needs to be validated.

In recent years, thanks to collaborative efforts and technological advances, different research groups performed pan-genomic studies that allowed a significant improvement in knowledge of

pathogenic mechanisms involved in adrenal tumour development and progression as well as in steroid autonomous secretion (8-11). For instance, in the field of ACA, somatic *PRKACA* mutations have been only recently reported to be involved in the pathogenesis of 35-65% of cortisol-producing adenomas (CPA) associated with overt Cushing syndrome (12). Thanks to this finding, we are now aware that the pathogenesis of up to 60% of CPA is due to genetic alterations in the cAMP/PKA pathway (i.e. affecting *PRKACA* and *GNAS* genes). Moreover, somatic mutations in *KCNJ5* (K⁺ channel), *ATP1A1* (Na⁺K⁺-ATPase), *ATP2B3* (Ca²⁺-ATPase) and *CANCAID* (Ca²⁺ channel, L type), have been recently found to be associated with the pathogenesis of 40-70% of aldosterone-producing adenomas (APA) (13).

Despite these important improvements in terms of molecular pathogenesis, many clinically-relevant questions on ACA still remain unanswered. For instance: How can we accurately diagnose the presence of a clinically unapparent (“subclinical” or mild) cortisol excess (Cushing syndrome) in patients affected by CPA? Which are the clinical implications and consequences of the presence of autonomous cortisol secretion in absence of overt clinical symptoms? Which are the best strategies for the management of patients with incidentally discovered endocrine inactive adenomas or with “subclinical” CPA?

Considering the ACC, novel genetic alterations have been discovered to be involved in their pathogenesis (e.g. in genes *ZNRF3*, *DAXX*, *TERT*, *MED12*, *PRKARIA*, *RPL22*, *TERF2*, *CCNE1*, and *NFI*) and/or associated with more aggressive behaviour and worst prognosis (8, 9). However, fully reliable and easy-applicable clinical and molecular prognostic factors for patients with ACC are still missing. In addition, up to date, only few pharmacological treatments are available for patients with advanced ACC. Some previous studies aimed to identify potential drug targets that might be useful for innovative therapeutic approaches in patients with advanced ACC, unfortunately without satisfying results (14, 15). On this connection, a very recent paper from our group demonstrated that targeted molecular profiling of tumor samples on formalin-fixed paraffin-embedded specimens is feasible and able to simultaneously improve prognostication of ACC beyond clinical/histopathological parameters and identify new potential drug targets (16). These findings might then pave the way to a precision medicine approach to ACC.

To summarise, basic and translational research on adrenocortical tumors is an active field that generated very promising advances during the last few years. Prominent examples include an improved understanding of adrenal tumor molecular pathogenesis as well as the introduction of new potential diagnostic and prognostic biomarkers. International collaboration as well as the use of innovative technology will be key factors to accelerate improvements in our knowledge of pathogenic mechanisms and in our skills for better diagnosis, prognosis and treatment of patients with these tumors. This will be possible only through joint efforts especially both within the European (European Network for the Study of Adrenocortical Tumours ENSAT, <http://www.ensat.org/>) and the extra-European community ([The American-Australian-Asian Adrenal Alliance A5,
https://elselab.wordpress.com/a5/](http://www.a5alliance.org/)). However, at the moment, routine management strategy for adrenocortical tumours might be challenging in several steps and should be decided in the setting of a multidisciplinary team in expert centers.

In this special issue, we present a number of systemic reviews focusing on the state-of-the-art about pathogenesis, diagnosis, prognosis and treatment of unilateral adrenocortical tumours focusing on non-aldosterone-producing ones. The Authors also give specific insights into future approaches proposed to improve the management of patients with adrenocortical tumours.

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